Journal of Critical Care 42 (2017) 18–24

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Clinical Potpourri

A multifactor model for predicting mortality in critically ill patients: A multicenter prospective cohort study

Zhongwang Li [a,1], Baoli Cheng [a,1], Jingya Wang [a], Guohao Xie [a], Xiaobo Yu [b], Man Huang [c], Zhijun Xu [c], Zhongqiu Lu [d], Huaqin Sun [e], Jian Zhang [f], Zhiyi Wang [g], Haiya Wu [h], Xu Liu [a], Lihua Chu [a], Jialian Zhao [a], Xiangming Fang [a,*]

[a] Department of Anesthesiology and Intensive Care Unit, The First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, PR China
[b] Department of Neurosurgery, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, PR China
[c] Intensive Care Unit, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, PR China
[d] Emergency Intensive Care Unit, The First Affiliated Hospital, Wenzhou Medical University, Wenzhou, Zhejiang, PR China
[e] Intensive Care Unit, The First Affiliated Hospital of Zhejiang Chinese Medicine University, Hangzhou, Zhejiang, PR China
[f] Intensive Care Unit, Hangzhou Normal University Affiliated Hospital, Hangzhou, Zhejiang, PR China
[g] Emergency Intensive Care Unit, The Second Affiliated Hospital, Wenzhou Medical University, Wenzhou, Zhejiang, PR China
[h] Intensive Care Unit, The Second Affiliated Hospital, Wenzhou Medical University, Wenzhou, Zhejiang, PR China

ARTICLE INFO

Keywords:
Intensive care unit (ICU)
Lactate
Neutrophil-to-lymphocyte ratio (NLR)
Acute physiology score (APS)
Charlson comorbidity index (CCI)
Mortality

ABSTRACT

Purpose: The objective of this study was to develop a model using a combination of routine clinical variables to predict mortality in critically ill patients.
Methods: A cohort of 500 patients recruited from eight university hospital intensive care units (ICUs) was used to develop a model via logistic regression analyses. Discrimination and calibration analyses were performed to assess the model.
Results: The model included the lactate level (odds ratio [OR] = 1.11, 95% confidence interval [CI] 1.01 to 1.22, $P = 0.029$), neutrophil-to-lymphocyte ratio (OR = 1.03, 95% CI 1.01 to 1.04, $P = 0.002$), acute physiology score (OR = 1.11, 95% CI 1.06 to 1.15, $P < 0.001$), Charlson comorbidity index (OR = 1.36, 95% CI 1.15 to 1.60, $P < 0.001$) and surgery type (OR: selective = Ref, no surgery = 8.04, 95% CI 3.74 to 17.30, $P < 0.001$, emergency = 3.66, 95% CI 1.60 to 8.36, $P = 0.002$). The model showed good discrimination (area under receiver operating characteristic curve: 0.84, 95% CI: 0.80 to 0.87) and calibration (Hosmer-Lemeshow test $P = 0.137$) for predicting in-hospital mortality.
Conclusion: The developed multifactor model can be used to effectively predict mortality in critically ill patients at ICU admission.

1. Introduction

Caring for critically ill patients causes massive burdens on healthcare systems. In the United States, the healthcare system uses nearly 5% of the national health expenditure to care for critically ill patients [1]. From 2002 to 2009, intensive care unit (ICU) admission had a mean biennial increase of 14.2% [2]. Moreover, despite the substantially increasing expenditures for critical illnesses, in-hospital mortality remains high (15%) in ICU, with a rate of 33% for critically ill patients with sepsis [1,3,4].

Although the Acute Physiology and Chronic Health Evaluation (APACHE) scoring system has developed to include scores from I to IV, the APACHE II score together with the Sequential Organ Failure Assessment (SOFA) Score and simplified acute physiology score (SAPS) are the most widely used approaches for predicting mortality in ICUs and play an important role in illness evaluations and clinical decision-making [5-7]. A meta-analysis showed that the APACHE II scoring system has the most accurate discrimination, with the highest pooled area under the receiver operating characteristic (ROC) curve (AUC) of 0.72 [8]. Nevertheless, there seems to be a large margin in which the prediction capacity can be raised.

Accumulated evidence has shown that many other factors are associated with fatal outcomes in critically ill patients. The Charlson comorbidity index (CCI) is the most widely applied score for measuring comorbidity and is reported to be associated with in-hospital mortality [9]. The neutrophil-to-lymphocyte ratio (NLR) is calculated as the

* Corresponding author at: Department of Anesthesiology, The First Affiliated Hospital of School of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou 310000, PR China.
E-mail address: xiangming_fang@163.com (X. Fang).
[1] These authors made equal contributions.

http://dx.doi.org/10.1016/j.jcrc.2017.06.015
0883-9441/

neutrophil count divided by the lymphocyte count, and previous studies have reported that the NLR is associated with the mortality of critically ill patients [10,11]. As a marker that is widely used to indicate the level of tissue perfusion, the arterial blood lactate concentration can be applied in critically ill patients as an outcome predictor [12,13]. The acute physiology abnormality is a major part of the APACHE scoring system contributing 65.6% to the prediction of in-hospital mortality [14]. To date, no data are available on the combined use of the lactate level, NLR, acute physiology score (APS) and CCI to predict mortality in critically ill patients.

Therefore, the present multicenter prospective study was designed to develop a multifactor model for predicting in-hospital mortality using multivariable logistic regression. We also assessed the calibration and discrimination of the multifactor model and compared them with those of the APACHE II and SOFA scores, as well as the outcomes across patient subgroups.

2. Methods

2.1. Study design and setting

This was a multicenter prospective cohort study intended to develop a model for predicting mortality in critically ill patients using an Access-based (AB) database. The present study was conducted in eight ICUs from six university-affiliated hospitals (approximately 13,170 beds) in Zhejiang Province in eastern China. Patients ($n = 500$) enrolled in the cohort were recruited from the aforementioned ICUs. The present study followed the principles of the Declaration of Helsinki received ethical approval from the Ethical Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (No. 2014319); the requirement for informed consent was waived because of the observational design.

2.2. Patient population

Critically ill patients consecutively admitted to ICUs from March 1, 2014 to April 30, 2014 were enrolled, except for those from the ICU of the Second Affiliated Hospital of the Zhejiang University School of Medicine who were relocated from June 1, 2014 to July 30, 2014. The following exclusion criteria were used: [1] patients younger than 18 years old; [2] an ICU stay <24 h; [3] patients with agranulocytosis whose absolute neutrophil count was $<0.5 \times 10^9$/L [15]; [4] patients without a lactate value within the 24 h after admission; [5] missing data; and [6] repeated admission (i.e., only the first admission would be included if a patient was admitted to the same ICU more than once). All enrolled patients were followed for at least 28 days.

2.3. Data collection

Data were collected from patients' medical records. The extracted parameters included demographic data, admission status data (admission source, surgery type, mechanical ventilation, immune status, CCI, APACHE II score, SOFA score, severe sepsis and cardio-pulmonary resuscitation [CPR] before ICU admission), laboratory data (white blood cell [WBC] count, neutrophil percentage [N%], lymphocyte percentage [L%], monocyte percentage [M%], lactate level, NLR, C-reactive protein [CRP] level and procalcitonin [PCT] level) and treatment data (nosocomial infection, ventilation duration, accumulated antimicrobial duration, length of stay [LOS] in ICU and hospital, and mortality [in hospital and within 30 days]). An infection was defined as either the invasion of tissue, body fluids, or a body cavity by a pathogenic microorganism or a clinically suspected infection; treatment involved the administration of antimicrobials [16,17]. Severe sepsis was defined as an infection inducing acute organ dysfunction [17]. A framework of comprehensively considered quality control strategies was were also used in this study. To ensure accurate and consistent measurements in this multicenter study, a manual of operations was used to maintain the same procedures and methodologies across the centers. In addition, the principle investigators supervised the fieldwork, identified and decided on the necessary amendments of the study protocol, and then, coordinated all the trainings session to ensure the accuracy of the data and the consistency of the procedures across the centers. Data were stored in an AB database. Additionally, two trained observers randomly extracted 10% of the cases from the database to check the integrity, accuracy and logic of the information.

2.4. Laboratory examinations

Patient samples of venous (3–5 mL) and arterial (1 mL) blood were collected upon ICU admission. Full blood cell counts were determined using a Sysmex XE-2100 hematology automated analyzer (Sysmex Corporation, Kobe, Japan). The NLR was calculated by dividing the neutrophil count by the lymphocyte count. A Hitachi Labospect 008 automated analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan) was used to measure CRP levels. A Roche Analytics E170 module immunology analyzer (Roche Diagnostics, Basel, Switzerland) was used to measure PCT levels, and a GEM Premier 3000 automatic blood gas analyzer (Instrumentation Laboratory Company, Lexington, USA) was used to measure arterial lactate concentrations.

2.5. Outcomes

All-cause in-hospital deaths were the primary outcome. Death within 30 days after admission, hospital acquired infection (HAI), ventilation duration, and LOS in the ICU and hospital were the secondary outcomes. A HAI was defined as a localized or systemic patient condition resulting from an infectious pathogen or its toxin(s) that was not present or incubating at the time of admission to the acute care setting [18].

2.6. Statistical analysis

Statistical analyses were performed using SPSS 20.0 (IBM Corporation, Chicago, USA), RStudio (version 0.99.489), GraphPad Prism 6.0 (GraphPad software, California, USA) and Microsoft Excel Plus 2013 (Microsoft Corporation, Washington, USA). Appropriate descriptive statistics are shown for the data types and distributions. The Kolmogorov–Smirnov test was used to assess the normality of the distributions of quantitative variables. For categorical variables, data are expressed the number and percentage; for quantitative variables, normally distributed data are presented as the mean ± standard deviation (SD), and non-normally distributed data are expressed as the median and interquartile range (IQR).

Univariate analyses were first performed to identify possible covariates related to sepsis. To reduce the number of false-positive results, only variables with $P < 0.1$ were subsequently entered into the multivariable logistic regression model using the forward conditional stepwise approach. The Hosmer-Lemeshow test was used to assess the calibration of the model. The ROC curves used death compared with in-hospital survival as the outcome for analyses [19]. Additionally, DeLong's test was used to compare the areas under the ROC curves (AUCs) [20].

Moreover, patients were categorized into three subgroups based on the quintiles of the predicted risk. The first and second quintiles were labeled low risk, the third and fourth quintiles were labeled medium risk, and the fifth quintile was labeled high risk. The cumulative death probability curves were assessed for patients with low, medium, and high risks by a Kaplan-Meier curve analysis. One-way ANOVA and chi-square tests were used to assess differences in the outcomes across these three subgroups. A two-tailed P-value <0.05 was considered statistically significant.